

Claims

1. Epothilone derivatives of general formula I,



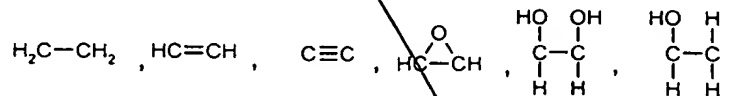
in which

~~R^{1a}, R^{1b} are the same or different and mean hydrogen, C₁-C₁₀ alkyl, aryl, C₇-C₂₀ aralkyl, or together a -(CH₂)_m group with m = 2, 3, 4 or 5,~~

~~R^{2a}, R^{2b} are the same or different and mean hydrogen, C₁-C₁₀ alkyl, aryl, C₇-C₂₀ aralkyl or together a -(CH₂)_n group with n = 2, 3, 4 or 5, whereby, if -D-E- stands for -CH₂-CH₂- or Y stands for an oxygen atom, R^{2a}/R^{2b} cannot be hydrogen/methyl,~~

R³ means hydrogen, C₁-C₁₀ alkyl, aryl, C₇-C₂₀ aralkyl,

~~R^{4a}, R^{4b} are the same or different and mean hydrogen, C₁-C₁₀ alkyl, aryl, C₇-C₂₀ aralkyl or together a -(CH₂)_p group with p = 2, 3, 4 or 5,~~



D-E means a group

R⁵ means hydrogen, C₁-C₁₀ alkyl, aryl, C₇-C₂₀ aralkyl,

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R^6 , R^7 each mean a hydrogen atom, together an additional bond or an oxygen atom,

R^8 means hydrogen, C_1 - C_{20} alkyl, aryl, C_7 - C_{20} aralkyl, which can all be substituted,

X means an oxygen atom, two alkoxy groups OR^{23} , a C_2 - C_{10} alkylene- α,ω -dioxy group, which can be straight-chain or branched, H/OR^9 or a grouping $CR^{10}R^{11}$, whereby

R^{23} stands for a C_1 - C_{20} alkyl radical,

R^9 stands for hydrogen or a protective group PG^x ,

R^{10} , R^{11} are the same or different and stand for hydrogen, a C_1 - C_{20} alkyl, aryl, C_7 - C_{20} aralkyl radical or R^{10} and R^{11} together with the methylene carbon atom together stand for a 5- to 7-membered carbocyclic ring,

Y means an oxygen atom or two hydrogen atoms,

Z means an oxygen atom or H/OR^{12} ,

whereby

R^{12} means hydrogen or a protective group PG^z .

2. Epothilone derivatives of general formula I according to claim 1, in which Y, Z, R^{1a} , R^{1b} , R^{2a} and R^{2b} all can have the meanings that are indicated in general formula I, and the remainder of the molecule is identical to naturally occurring epothilone A or B.

3. Epothilone derivatives of general formula I according to claim 1, in which R^3 , R^{4a} , R^{4b} , D-E, R^5 , R^6 and R^7 all can have the meanings that are indicated in general formula I, and the

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remainder of the molecule is identical to naturally occurring epothilone A or B.

4. Epothilone derivatives of general formula I according to claim 1, in which R^6 , R^7 , R^8 and X all can have the meanings that are indicated in general formula I, and the remainder of the molecule is identical to naturally occurring epothilone A or B.

5. Epothilone derivatives of general formula I according to claim 1, in which Y, Z, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , D-E, R^5 , R^6 and R^7 all can have the meanings that are indicated in general formula I, and the remainder of the molecule is identical to naturally occurring epothilone A or B.

6. Epothilone derivatives of general formula I according to claim 1, in which Y, Z, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^6 , R^7 , R^8 and X all can have the meanings that are indicated in general formula I, and the remainder of the molecule is identical to naturally occurring epothilone A or B.

7. Epothilone derivatives of general formula I according to claim 1, in which R^3 , R^{4a} , R^{4b} , D-E, R^5 , R^6 , R^7 , R^8 and X all can have the meanings that are indicated in general formula I, and the remainder of the molecule is identical to naturally occurring epothilone A or B.

8. Compounds of general formula I, namely

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione, and

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(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione (B)

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and

(1R,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and

(1R,3S(E),7S,10R,11S,12S,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7S,8R,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione and

(4S,7S,8R,9S,13E,16S(E))-4,8-dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10S,11R,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-

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4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione, and

(1R,3S(E),7S,10S,11R,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1S,3S(E),7S,10S,11R,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione, and

(1R,3S(E),7S,10S,11R,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-((3-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione, and

(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-((3-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-((3-pyridyl)ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione, and

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-((3-pyridyl)ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

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(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-((4-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione, and

(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-((4-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-((4-pyridyl)ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione, and

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-((4-pyridyl)ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-7-phenyl-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-phenyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-phenyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

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(4S,7R,8S,9S,13(E or Z),16S(E))-7-Benzyl-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-10-Benzyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-10-Benzyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,13-tetramethyl-9-trifluoromethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,16-tetramethyl-12-trifluoromethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,16-tetramethyl-12-trifluoromethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

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(4S,7R,8S,9S,11E/Z,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-11,13-diene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,14E/Z,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,14E/Z,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-11-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9-tetramethyl-13-trifluoromethyl-cyclohexadec-13-ene-2,6-dione

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(1(S or R), 3S(E), 7S, 10R, 11S, 12S, 16R)-7, 11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8, 8, 10, 12-tetramethyl-16-trifluoromethyl-4, 17-dioxabicyclo[14.1.0]heptadeca-5, 9-dione

(1(R or S), 3S(E), 7S, 10R, 11S, 12S, 16S)-7, 11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8, 8, 10, 12-tetramethyl-16-trifluoromethyl-4, 17-dioxabicyclo[14.1.0]heptadeca-5, 9-dione

(4S, 7R, 8S, 9S, 13(E or Z), 16S(E))-4, 8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-13-pentafluoroethyl-5, 5, 7, 9-tetramethyl-cyclohexadec-13-ene-2, 6-dione

(1(S or R), 3S(E), 7S, 10R, 11S, 12S, 16R)-7, 11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-16-pentafluoroethyl-8, 8, 10, 12-tetramethyl-4, 17-dioxabicyclo[14.1.0]heptadeca-5, 9-dione

(1(R or S), 3S(E), 7S, 10R, 11S, 12S, 16S)-7, 11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-16-pentafluoroethyl-8, 8, 10, 12-tetramethyl-4, 17-dioxabicyclo[14.1.0]heptadeca-5, 9-dione

(4S, 7R, 8S, 9S, 13(E or Z), 16S(E))-4, 8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5, 5-(1, 3-trimethylene)-7, 9, 13-trimethyl-cyclohexadec-13-ene-2, 6-dione

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(1(S or R), 3S(E), 7S, 10R, 11S, 12S, 16R)-7, 11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8, 8-(1, 3-trimethylene)-10, 12, 16-trimethyl-4, 17-dioxabicyclo[14.1.0]heptadeca-5, 9-dione

(1(R or S), 3S(E), 7S, 10R, 11S, 12S, 16S)-7, 11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8, 8-(1, 3-trimethylene)-10, 12, 16-trimethyl-4, 17-dioxabicyclo[14.1.0]heptadeca-5, 9-dione

(4S, 7R, 8S, 9S, 11E/Z, 13(E or Z), 16S(E))-4, 8-Dihydroxy-13-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5, 5, 7, 9-tetramethyl-cyclohexadec-11, 13-diene-2, 6-dione

(1(S or R), 3S(E), 7S, 10R, 11S, 12S, 14E/Z, 16R)-7, 11-Dihydroxy-16-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8, 8, 10, 12-tetramethyl-4, 17-dioxabicyclo[14.1.0]heptadec-14-ene-5, 9-dione

(1(R or S), 3S(E), 7S, 10R, 11S, 12S, 14E/Z, 16S)-7, 11-Dihydroxy-16-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8, 8, 10, 12-tetramethyl-4, 17-dioxabicyclo[14.1.0]heptadec-14-ene-5, 9-dione

(4S, 7R, 8S, 9S, 11E/Z, 13(E or Z), 16S(E))-4, 8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-13-propyl-5, 5, 7, 9-tetramethyl-cyclohexadec-11, 13-diene-2, 6-dione

(1(S or R), 3S(E), 7S, 10R, 11S, 12S, 14E/Z, 16R)-7, 11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-16-propyl-8, 8, 10, 12-tetramethyl-4, 17-dioxabicyclo[14.1.0]heptadec-14-ene-5, 9-dione

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(1(R or S), 3S(E), 7S, 10R, 11S, 12S, 14E/Z, 16S)-7, 11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-16-propyl-8, 8, 10, 12-tetramethyl-4, 17-dioxabicyclo[14.1.0]heptadec-14-ene-5, 9-dione

(4S, 7R, 8S, 9S, 13(E or Z), 16S(E))-4, 8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5, 5, 7, 9, 13-pentamethyl-cyclohexadec-13-ene-2, 6-dione

(1(S or R), 3S(E), 7S, 10R, 11S, 12S, 16R)-7, 11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8, 8, 10, 12, 16-pentamethyl-4, 17-dioxabicyclo[14.1.0]heptadecane-5, 9-dione

(1(R or S), 3S(E), 7S, 10R, 11S, 12S, 16S)-7, 11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8, 8, 10, 12, 16-pentamethyl-4, 17-dioxabicyclo[14.1.0]heptadecane-5, 9-dione

(4S, 7R, 8S, 9S, 13(E or Z), 16S(E))-4, 8-Dihydroxy-16-(1-methyl-2-(4-pyridyl)ethenyl)-1-oxa-5, 5, 7, 9, 13-pentamethyl-cyclohexadec-13-ene-2, 6-dione

(1(S or R), 3S(E), 7S, 10R, 11S, 12S, 16R)-7, 11-Dihydroxy-3-(1-methyl-2-(4-pyridyl)ethenyl)-8, 8, 10, 12, 16-pentamethyl-4, 17-dioxabicyclo[14.1.0]heptadecane-5, 9-dione

(1(R or S), 3S(E), 7S, 10R, 11S, 12S, 16S)-7, 11-Dihydroxy-3-(1-methyl-2-(4-pyridyl)ethenyl)-8, 8, 10, 12, 16-pentamethyl-4, 17-dioxabicyclo[14.1.0]heptadecane-5, 9-dione

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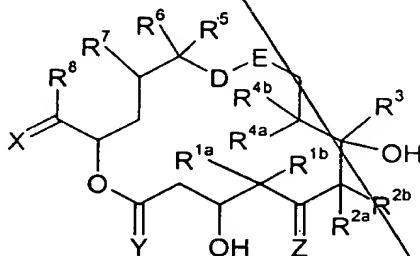
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(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-6-one

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-9-one

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-9-one.

9. Process for the production of epothilone derivatives of general formula I according to claim 1



in which

the substituents have the meanings that are indicated in general formula I, characterized in that

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Discussion

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1. The first step is to identify the problem or question that needs to be addressed. This involves understanding the context and the specific requirements of the task.

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in which

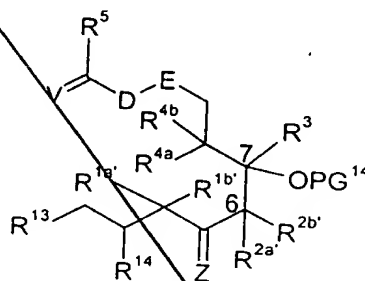
$R^{3'}$, $R^{4a'}$, $R^{4b'}$ and $R^{5'}$ have the meanings already mentioned for R^3 , R^{4a} , R^{4b} and R^5 , and

V means an oxygen atom, two alkoxy groups OR^{17} , a C_2-C_{10} alkylene- α,ω -dioxo group, which can be straight-chain or branched or H/OR^{16} ,

W means an oxygen atom, two alkoxy groups OR^{19} , a C_2-C_{10} alkylene- α,ω -dioxo group, which can be straight-chain or branched or H/OR^{18} ,

R^{16} , R^{18} , independently of one another, mean hydrogen or a protective group PG^1

R^{17} , R^{19} , independently of one another, mean C_1-C_{20} alkyl, to a partial fragment of general formula AB

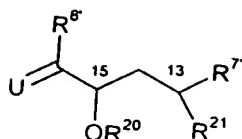


AB,

in which $R^{1a'}$, $R^{1b'}$, $R^{2a'}$, $R^{2b'}$, R^3 , R^{4a} , R^{4b} , R^5 , R^{13} , R^{14} , D, E, V and Z have the meanings already mentioned, and PG^{14} represents a hydrogen atom or a protective group PG, and this partial fragment AB is reacted with a fragment of

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general formula C



C

in which

- R^8 has the meaning already mentioned in general formula I for R^8 , and
- R^7 means a hydrogen atom,
- R^{20} means a hydrogen atom or a protective group PG^2 ,
- R^{21} means a hydroxy group, halogen, a protected hydroxy group OPG^3 , a phosphonium halide radical $PPh_3^+Hal^-$ (Ph = phenyl; Hal = F, Cl, Br, I), a phosphonate radical $P(O)(OQ)_2$ (Q = C_1 - C_{10} alkyl or phenyl) or a phosphine oxide radical $P(O)Ph_2$ (Ph = phenyl),
- U means an oxygen atom, two alkoxy groups OR^{23} , a C_2 - C_{10} alkylene- α,ω -dioxy group, which can be straight-chain or branched, H/ OR^9 or a grouping $CR^{10}R^{11}$,
- whereby
- R^{23} stands for a C_1 - C_{20} alkyl radical,
- R^9 stands for hydrogen or a protective group PG^3 ,
- R^{10} , R^{11} are the same or different and stand for hydrogen, a C_1 - C_{20} alkyl, aryl, C_7 - C_{20} aralkyl radical or R^{10} and R^{11} together with the methylene

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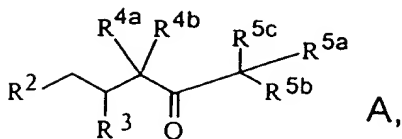
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10. Pharmaceutical preparations that contain at least one compound of general formula I according to claim 1, as well as a pharmaceutically compatible vehicle.

12. Process for the production of compounds of general

12. Process for the production of compounds of general



R^2 means CH_2OR^{2a} , CHO , CO_2R^{2b} , COX ,

~~R^{2a}, R^{2b} mean hydrogen, C₁-C₂₀ alkyl, aryl, C₇-C₂₀ aralkyl,~~

~~R³ means hydrogen, OR^{3a}, X, OSO₂R^{3b},~~

~~R^{3a} means hydrogen or together with R^{2a} a -(CH₂)_n group or a CR^{6a}R^{6b} group,~~

R^{3b} means C₁-C₄ alkyl, aryl,

X means halogen,

n means 2 to 4,

~~R^{6a}, R^{6b} are the same or different and mean C₁-C₈ alkyl, C₆-C₁₀ aryl or together a -(CH₂)_o group,~~

o means 3 to 6,

R^{6a} additionally can assume the meaning of hydrogen,

R^{4a} , R^{4b} are the same or different and mean hydrogen, C_1 - C_{10} alkyl, C_7 - C_{20} aralkyl or together a $-(CH_2)_m$ group,

m means 2 to 5,

~~R^{5a}, R^{5b} are the same or different and mean hydrogen, C₁-C₁₀
alkyl, C₇-C₂₀ aralkyl or together a -(CH₂)_p group,~~

p means 2 to 5,

R^{5c} means hydrogen,

~~including all stereoisomers and mixtures thereof,~~

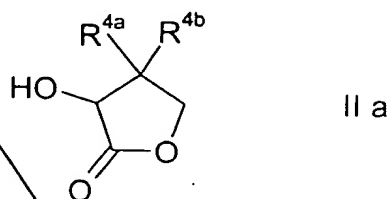
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free hydroxyl groups can be etherified or esterified in R^2 and R^3 , free carbonyl groups can be ketalized in A and R^2 , converted into an enol ether or reduced, and free acid groups in A can be converted into their salts with bases, wherein

a) a pantolactone of general formula IIa or



in which

R^{4a} and R^{4b} in each case are methyl groups or

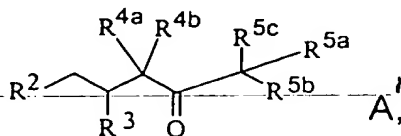
b) a malonic acid dialkyl ester of general formula XXVIII



in which

R^{4a} , R^{4b} , which have the meaning that is indicated in general formula A, and alkyl, independently of one another, mean a C_1 - C_{20} alkyl, C_3 - C_{10} cycloalkyl or C_4 - C_{20} alkylcycloalkyl radical, is used as a starting product.

13. Compounds of general formula A'



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in which

R^2 means CH_2OR^{2a} , CHO , CO_2R^{2b} , COX ,

R^{2a} , R^{2b} mean hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl,

R^3 means hydrogen, OR^{3a} , X , OSO_2R^{3b} ,

R^{3a} means hydrogen or together with R^{2a} a $-(CH_2)_n$ group or a $CR^{6a}R^{6b}$ group,

R^{3b} means C_1-C_4 alkyl, aryl,

X means halogen,

n means 2 to 4,

R^{6a} , R^{6b} are the same or different and mean C_1-C_8 alkyl, C_6-C_{10} aryl or together a $-(CH_2)_o$ group,

o means 3 to 6,

R^{6a} additionally can assume the meaning of hydrogen,

R^{4a} , R^{4b} are the same or different and mean hydrogen, C_1-C_{10} alkyl, C_7-C_{20} aralkyl or together a $-(CH_2)_m$ group,

m means 2 to 5,

R^{5a} , R^{5b} are the same or different and mean hydrogen, C_1-C_{10} alkyl, C_7-C_{20} aralkyl or together a $-(CH_2)_p$ group,

p means 2 to 5,

R^{5c} means hydrogen,

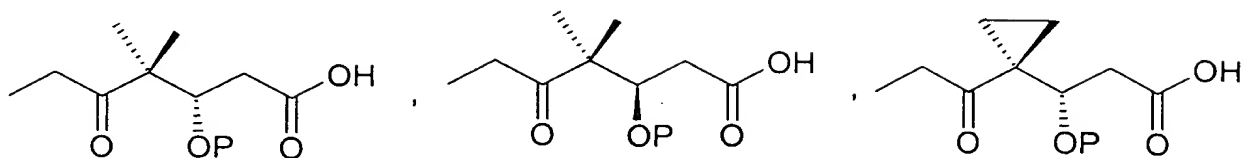
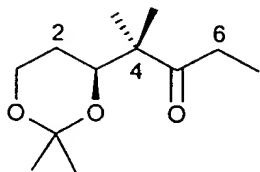
including all stereoisomers and mixtures thereof,

and

free hydroxyl groups can be etherified or esterified in R^2 and R^3 , free carbonyl groups can be ketalized in A and R^2 , converted into an enol ether or reduced, and free acid groups in A can be converted into their salts with bases,

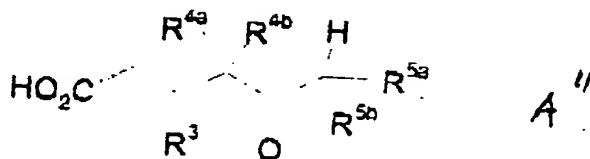
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excluding the compounds



P = TBS

14. Process for the production of compounds of general formula A''



in which

R^3 means OR^{3a} and

R^{3a} means hydrogen or a protective group PG

R^{4a} , R^{4b} are the same or different and mean hydrogen,

C_1 - C_{10} -alkyl, C_7 - C_{20} -aralkyl, or together a $-(CH_2)_m$ group,

m means 2-5,

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R^{5a} , R^{5b} are the same or different and mean hydrogen,
 C_1-C_{10} -alkyl, C_7-C_{20} -aralkyl, or together a $-(CH_2)_p$
 group,

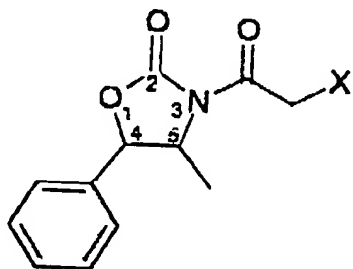
p means 2-5,

including all stereoisomers and mixtures thereof,

and

free carbonyl groups can be ketalized in A",

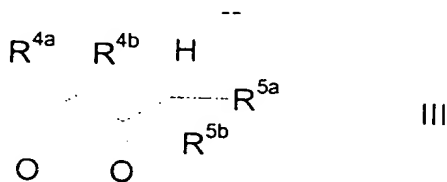
wherein a compound of general formula II



II

in which

X is a chlorine or bromine atom, and the 2-oxazolidinone
 ring has either a (4R,5S) or a (4S,5R) conformation,
 is reacted with a compound of general formula III



III

in which

R^{4a} , R^{4b} are the same or different and mean hydrogen,

C_1-C_{10} -alkyl, C_7-C_{20} -aralkyl, or together a $-(CH_2)_m$ group,

m means 2-5,

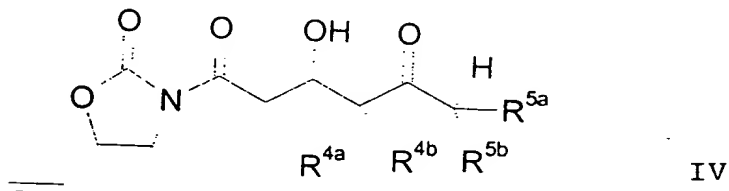
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R^{5a} , R^{5b} are the same or different and mean hydrogen,

C₁-C₁₀-alkyl, C₇-C₂₀-aralkyl, or together a -(CH₂)_p group,

p means 2-5,

to a compound of general formula IV



in which

the 2-oxazolidinone ring (4R,5S) and the 3'-carbon atom have an R conformation, or

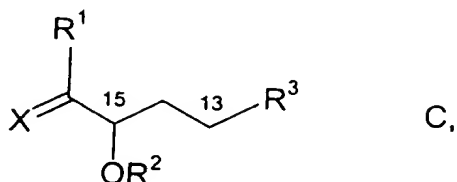
the 2-oxazolidinone ring (4*S*,5*R*) and the 3'-carbon atom have an *S* conformation,

the 3'-hydroxy group in IV is protected by a protective group PG, the oxazolidinone ring is cleaved, and protective group PG is optionally cleaved.

15. Process according to claim 14, wherein the compound of general formula II is reacted in the presence of chromium(II) chloride with a compound of general formula III.

16. Process according to claim 14 or 15, wherein the cleaved oxazolidinone ring is recovered in an enantiomer-pure manner.

17/ Compounds of general formula C



in which

R^1 means hydrogen, C_1 - C_{20} alkyl, aryl, C_7 - C_{20} aralkyl, which can all be substituted,

R^2 means hydrogen or a protective group PG^1 ,

R^3 means a hydroxy group, halogen, a protected hydroxy group OPG^2 , a phosphonium halide radical $PPh_3^+Hal^-$ (Ph = phenyl; Hal = F, Cl, Br, I), a phosphonate radical $P(O)(OQ)_2$ ($Q = C_1$ - C_{10} alkyl or phenyl) or a phosphine oxide radical $P(O)Ph_2$ (Ph = phenyl),

X means an oxygen atom, two alkoxy groups OR^4 , a C_2 - C_{10} alkylene- α,ω -dioxy group, which can be straight-chain or branched, H/OR^5 or a grouping CR^6R^7 ,
whereby

R^4 stands for a C_1 - C_{20} alkyl radical,

R^5 stands for hydrogen or a protective group PG^3 ,

R^6, R^7 are the same or different and stand for

hydrogen, a C_1 - C_{20} alkyl, aryl, C_7 - C_{20} aralkyl radical or R^6 and R^7 together with the methylene carbon atom together stand for a 5- to 7-membered carbocyclic ring,

whereby not simultaneously

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21. Compounds of general formula C according to claim 20,
wherein the aryl radical that stands for R⁶ and/or R⁷ is selected
from the group 2-, 3-furanyl; 2-, 3-, 4-pyridinyl; 2-, 4-, 5-

thiazolyl; 2-, 4- and 5-imidazolyl radical, which optionally is substituted by 1 or 2 C₁-C₄ alkyl radicals.

22. Compounds of general formula C according to claim 17, wherein protective groups PG¹, PG², and PG³ are selected from the group of substituents methoxymethyl, methoxyethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl, benzyl, para-nitrobenzyl, para-methoxybenzyl, formyl, acetyl, propionyl, isopropionyl, pivalyl, butyryl, or benzoyl radical.

23. Compounds according to claim 18, wherein protective group PG⁴ is selected from the group of substituents methoxymethyl, methoxyethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl, benzyl, para-nitrobenzyl, para-methoxybenzyl, formyl, acetyl, propionyl, isopropionyl, pivalyl, butyryl or benzoyl radical.

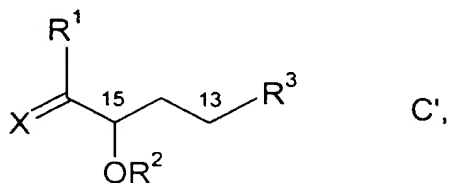
24. Compounds according to claim 20, wherein protective group PG⁵ is selected from the group of substituents methoxymethyl, methoxyethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl, benzyl, para-nitrobenzyl, para-methoxybenzyl, formyl, acetyl, propionyl, isopropionyl, pivalyl, butyryl or benzoyl radical.

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25. Compounds according to claim 22, wherein protective group PG¹ is a tert-butyldiphenylsilyl, tert-butyldimethylsilyl or triisopropylsilyl radical.

26. Compounds according to claim 22, wherein protective group PG² is a tert-butyldimethylsilyl, acetyl, benzoyl, benzyl or tetrahydropyranyl radical.

27. Process for the production of compounds of general formula C'



in which

R¹ means hydrogen, C₁-C₂₀ alkyl, aryl, C₇-C₂₀ aralkyl, which can all be substituted,

R² means hydrogen or a protective group PG¹,

R³ means a hydroxy group, halogen, a protected hydroxy group OPG², a phosphonium halide radical PPh₃⁺Hal⁻ (Ph = phenyl; Hal = F, Cl, Br, I), a phosphonate radical P(O)(OQ)₂ (Q=C₁-C₁₀ alkyl or phenyl) or a phosphine oxide radical P(O)Ph₂ (Ph = phenyl),

X means an oxygen atom, two alkoxy groups OR⁴, a C₂-C₁₀ alkylene-α,ω-dioxy group, which can be straight-chain or branched, H/OR⁵ or a grouping CR⁶R⁷,

whereby

R⁴ stands for a C₁-C₂₀ alkyl radical,

R⁵ stands for hydrogen or a protective group PG³,

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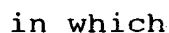
hydrogen, a C₁-C₂₀ alkyl, aryl, C₇-C₂₀ aralkyl radical or R⁶ and R⁷ together with the methylene carbon atom together stand for a 5- to 7-membered carbocyclic ring,

28. Process according to claim 27, wherein L-(-)-malic acid or D-(+)-malic acid is used.

$$\begin{array}{c} \text{R}^1 \\ | \\ \text{R}^5\text{O}-\text{C}-\text{CH}_2-\text{CH}_2-\text{OPG}^{2+\text{H}} \\ | \\ \text{OPG}^1 \end{array} \quad \text{VI}''$$

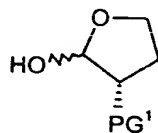
R^1 , PG^1 and R^5 have the meaning that is indicated in general formula C, and

30. Process for the production of the compounds of general formula VI" according to claim 29, wherein an organometal compound of general formula



Y stands for an alkali metal atom or MZ, whereby M is a divalent metal atom and Z is a halogen atom,

is added to a compound of general Formula IV

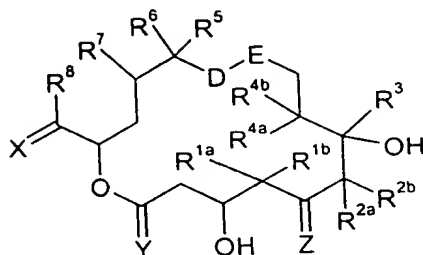


in which

PG¹ has the meaning that is indicated in general Formula C, while the lactol ring is opened, and then optionally the primary hydroxy group is protected with a protective group PG² and optionally the secondary group is protected with a protective group PG³.

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This invention relates to the new epothilone derivatives of general formula I,



1.

in which

substituents Y, Z, R^{2a}, R^{2b}, R³, R^{4a}, R^{4b}, D-E, R⁵, R⁶, R⁷, R⁸ and X have the meanings that are indicated in more detail in the description.

The new compounds interact with tubulin by stabilizing microtubuli that are formed. They are able to influence the cell-splitting in a phase-specific manner and are suitable for treating malignant tumors, for example, ovarian, stomach, colon, adeno-, breast, lung, head and neck carcinomas, malignant melanomas, acute lymphocytic and myelocytic leukemia. In addition, they are suitable for anti-angiogenesis therapy as well as for treatment of chronic inflammatory diseases (psoriasis, arthritis). To avoid uncontrolled proliferation of cells and for better compatibility of medical implants, they can be applied or introduced into polymer materials.

The compounds according to the invention can be used alone or to achieve additive or synergistic actions in combination with

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other principles and classes of substances that can be used in tumor therapy.

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